REMARKS/ARGUMENTS

The amendments to the specification, drawing and claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Prior to the present amendment, Claims 28-40 were pending in this application and were rejected on various grounds. Claim 37 has been cancelled without prejudice. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications. The rejection of the remaining claims is respectfully traversed.

Specification

The specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

The specification has been amended to capitalize all of the trademarks and to include a proper trademark symbol, such as ™ or ®, following the trademark as requested by the Examiner. In addition, Applicants respectfully submit that generic terminology can be found immediately following or adjacent to each use of a trademark (*e.g.,* in a sentence preceding or following the use of the trademark). Accordingly, Applicants respectfully submit that every effort has been made to prevent use of trademarks in any manner which might adversely affect their validity as trademarks.

Drawing

Figure 74 has been amended to correct a typographical error. In Figure 74, under the section titled "Transmembrane domains:", the amino acid residue numbers "217-287" have been amended to recite "271-287". Support for the amendment correcting the error can be found at least on p. 107, lines 29-31 and on p. 409, lines 25-26. A copy of the original Figure 74 showing the proposed change in red ink, together with a amended Figure 74 with the change made is enclosed herewith.

Priority

The Examiner stated that "this application is supported by the disclosure in application serial no. PCT/US00/04342, filed February 18, 2000 but is not supported by any of the earlier applications because no utility for the claimed polypeptide, PRO 1244, is disclosed in the earlier

applications." Applicants rely on the endothelial cell proliferation assay (Example 136, Assay #8) and the mouse kidney mesangial cell proliferation assay (Example 145, Assay #92) for support of patentable utility.

The data for the endothelial cell proliferation assay was first disclosed in Example 55 of International Application Serial No. PCT/US99/28313 filed on November 30, 1999, the priority of which is claimed in the present application. Example 55 on page 171 of the PCT publication, WO 00/32221, corresponding to PCT application, PCT/US99/28313, disclosing the endothelial cell proliferation assay, is enclosed herewith.

The data for the mouse kidney mesangial cell proliferation assay was first disclosed in International Application Serial No. PCT/US00/04342 filed on February 18, 2000, the priority of which is claimed in the present application.

Furthermore, Applicants respectfully submit herewith Declarations by Dr. Goddard and Dr. Wood stating that the claimed PRO1244 polypeptide sequence and its encoding nucleic acid sequence were obtained prior to August 14, 1998.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 28-33, 37, 39, and 40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner noted that "[t]he limitation that the encoded protein comprises an 'extracellular domain' ... 'lacking its associated signal peptide' (Claim 28, part (d), for example) is indefinite[.]"

Since the term "extracellular domain ... lacking its associated signal peptide" is no longer present in Claims 28-33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

Claim 37 has been cancelled without prejudice and hence, the rejection to this claim is believed to be moot, and should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 28-32, 39 and 40 are rejected under 35 U.S.C. §112, first paragraph, because "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these

claims."

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite "the polypeptide is capable of stimulating endothelial cell growth or the polypeptide is capable of inducing proliferation of kidney mesangial cells." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

In addition, the Examiner has admitted that the specification was "enabling for an isolated polypeptide having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO: 130, which isolated polypeptide stimulates adrenal cortical capillary endothelial cell (ACE) growth[.]" (See Office Action, p. 3). In addition, Examiner stated that the PRO1244 polypeptide "was shown to stimulate ACE growth (p.485, Example 136, Assay #8)" and "was also shown to induce proliferation of kidney mesangial cells (p. 505, Example 145, Assay #92)." (See Office Action, page 4). Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 28-32, 39 and 40 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner noted that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have

been amended to recite "the polypeptide is capable of stimulating endothelial cell growth or the polypeptide is capable of inducing proliferation of kidney mesangial cells." These biological activities, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §102

Claims 28-40 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 2003/0096951 (Jacobs *et al.*, publication date May 22, 2003 and effective filing date August 14, 1998).

Applicants thank Examiner Kapust for providing relevant pages from the priority document, provisional application 60/096,622 dated August 14, 1998, of U.S. Patent Publication No. 2003/0096951 disclosing SEQ ID NO: 4 in the publication.

In response, Applicants respectfully submit Declarations by Dr. Goddard and Dr. Wood, the consideration of which is respectfully requested.

Applicants simply need to disclose what is disclosed in the cited reference to support the priority claim

Applicants respectfully submit that the Declarations by Dr. Goddard and Dr. Wood ("Declarations") simply needs to provide a disclosure commensurate in scope with the disclosure in the priority document by Jacobs *et al.* to support the priority claim.

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating

that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

Accordingly, Applicants respectfully submit that the Declarations simply need to show possession of the polypeptide sequence disclosed in Jacobs *et al.* in order to remove Jacobs *et al.* as a prior art reference.

The cited Publication No. 2003/0096951 and the priority document 60/096,622 by Jacobs *et al.* disclose a polypeptide (SEQ ID NO: 4), which is identical to the PRO1244 polypeptide

sequence (SEQ ID NO: 130) of the present application. However, the cited Publication No. 2003/0096951 does not teach that the polypeptide of SEQ ID NO: 4 is capable of stimulating adrenal cortical capillary endothelial cell (ACE) growth or inducing proliferation of mammalian kidney mesangial cells. Accordingly, Publication No. 2003/0096951 and the priority document merely disclose the amino acid sequence identical to the PRO1244 polypeptide, but are devoid of any experimental data demonstrating the ACE growth stimulation activity or the mesangial cell proliferation induction activity as disclosed in the present application.

As shown in the Declarations, Applicants respectfully submit that Dr. Goddard and Dr. Wood, along with other inventors of the above-identified application, conceived and reduced to practice the PRO1244 polypeptide claimed in the present application in the United States prior to August 14, 1998.

As indicated in the Declarations and the brief description of Figure 73 of the present specification, the PRO1244 polypeptide is encoded by DNA 64883-1526.

Furthermore, as stated in the Declarations, the GSeqEdit database stores cloning and sequencing information for each PRO polypeptide and its encoding nucleic acid sequences according to its DNA number. Copies of the pages from the GSeqEdit database report (with the dates redacted) showing the cloning and sequencing information for the PRO1244 polypeptide sequences and its encoding nucleic acid sequence are attached to the Declarations as Exhibit A.

The GSeqEdit report shows the full length nucleic acid sequence for DNA-64883-1526 (identified as "DNA-64883") and the full length polypeptide sequence encoded by DNA 64883. As evidenced from the report and stated in the Declarations, both the nucleic acid and amino acid sequences shown in Exhibit A were obtained prior to August 14, 1998.

In addition, as stated in the Declarations, the DNA-64883 sequence shown in the GSeqEdit report is identical to the SEQ ID NO: 129 disclosed in the present application. The amino acid sequence shown in the GSeqEdit report is also identical to SEQ ID NO: 130 disclosed in the present application and to SEQ ID NO: 4 in Jacobs *et al.*

Accordingly, the attached Exhibit A clearly shows that Applicants were in possession of DNA-64883-1526 and the PRO1244 polypeptide encoded by DNA 64883-1526, as claimed in the present application, prior to August 14, 1998. Consequently, based on the teachings of *In re* Stempel and *In re* Moore, Applicants respectfully submit that Jacobs *et al.* is not prior art under

102(e) since its publication date and its effective filing date are after the effective priority date of the present application. Hence, Applicants respectfully request this rejection be withdrawn.

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2830 P1C7**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 25, 2004

By: _____
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day two, test samples (20 μl) containing the test PRO polypeptide are added. On day five, the cells are fixed and then stained. An increase in ANP message can also be measured by PCR from cells after a few hours. Results are based on a visual score of cell size: 0 = no inhibition, -1 =small inhibition, -2 = large inhibition. A score of less than 0 is considered positive. Activity reference corresponds to phenylephrin (PE) at 0.1 mM, as a positive control. A score of 2 is considered very responsive. Assay media included: M199 (modified)-glutamine free, $NaHCO_3$, phenol red, supplemented with 100 nM insulin, 0.2% BSA, 5 mM cretine, 2 mM L-carnitine, 5 mM taurine, 100 U/ml penicillin G, 100 μg/ml streptomycin (CCT medium). Only inner 60 wells are used in 96 well plates. Of these, 6 wells are reserved for negative and positive (PE) controls. Initially, quantitative PCR will be run in parallel to determine relative level of sensitivity to the visual scoring system.

PRO269 and PRO356 showed positive results in inhibition of heart adult hypertrophy in the above described assay.

EXAMPLE 55

Stimulation of Endothelial Cell Proliferation

This assay is designed to determine whether PRO polypeptides show the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth.

Bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample. (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO_2. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter: 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of a PRO polypeptide was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was $\geq$ 50% increase over background. VEGF (5 ng/ml) control at 1% dilution gave 1.24 fold stimulation; FGB (5 ng/ml) control at 1% dilution gave 1.46 fold stimulation.

PRO179, PRO212. PRO1075. PRO1154, PRO1244, PRO1286, and PRO1303 assayed "positive" as shown in TABLE 6 below:

FIGURE 74

MAARWRFWCVSVTMVVALLIVCDVPSASAQRKKEMVLSEKVSQLMEWTNKRPVIRMNGDKFR
RLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFFAMVDFDEG
SDVFQMLNMNSAPTFINFPAKGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPPNY
AGPLMLGLLLAVIGGLVYLRRSNMEFLFNKTGWAFAALCFVLAMTSGQMWNHIRGPPYAHKN
PHTGHVNYIHGSSQAQFVAETHIVLLFNGGVTLGMVLLCEAATSDMDIGKRKIMCVAGIGLV
VLFFSWMLSIFRSKYHGYPYSFLMS

Signal peptide:

amino acids 1-29

Transmembrane domains:

amino acids 183-205, 217-237, ~~217~~271-287, 301-321